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ORIGINAL ARTICLE

The role of ubiquitin C–terminal hydrolase (UCH-L1) and protein S100B in differentiating patients with epileptic and psychogenic non-epileptic seizures – Pilot study

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Abstract

Objective: Psychogenic non-epileptic seizures (PNES) are functional neurological disorders that are often misdiagnosed and treated as epileptic seizures (ES). Video-electroencephalography (v-EEG) is the gold standard for differentiating ES from PNES. However, blood biomarkers provide a faster and more accessible methodology, particularly for unwitnessed events. Ubiquitin C-terminal hydrolase L1 (UCH-L1) and protein S100B are key biomarkers released following neuronal and glial damage. Previous experimental and clinical studies have shown increased postictal serum and cerebrospinal fluid (CSF) levels of UCH-L1 and S100B in patients with ES.

Methods: This prospective cohort pilot study compared postictal serum levels of UCH-L1 and S100B proteins in subjects with ES to those with PNES, aiming to identify specific biomarkers for distinguishing these conditions. To exclude confounding factors, the inclusion criteria required normal magnetic resonance (MR) findings of the brain. Strict timing of blood sampling and v-EEG monitoring were used for diagnosing PNES. The study included 32 subjects with epilepsy, 36 with PNES, and 30 healthy controls.

Results: A significant difference in postictal UCH-L1 levels was observed among the groups. Subjects with ES had significantly higher postictal UCH-L1 levels (pg/mL) compared to those with PNES ($p = 0.049$) and healthy controls ($p = 0.029$). No significant differences were found between PNES subjects and healthy controls ($p = 0.756$). Postictal protein S100B levels did not differ significantly between the groups ($p = 0.515$).

Significance: This study confirms the potential of postictal UCH-L1 levels as a biomarker for distinguishing ES from PNES. However, it also raises questions about the utility of protein S100B as a biomarker in epilepsy. Given the pilot nature of this study, UCH-L1 cannot yet be adopted for clinical use due to the

small sample size, as statistical significance may have been driven by a subset of eight patients.

Plain Language Summary: This study evaluated two potential biomarkers, UCH-L1 and S100B, to differentiate ES from PNES in clinical practice. Our findings showed elevated postictal UCH-L1 levels in subjects with epilepsy compared to those with PNES, while no significant differences in S100B levels were observed among the groups.

KEYWORDS

epilepsy, protein S100B, psychogenic non-epileptic seizures, ubiquitin C-terminal hydrolase L1

1 | INTRODUCTION

Epilepsy is a chronic disorder of the central nervous system and one of the most prevalent neurological diseases. It is characterized by a predisposition to epileptic seizures (ES) and is associated with significant neurobiological, psychological, cognitive, and social consequences.[1–3] In contrast, psychogenic non-epileptic seizures (PNES) are functional neurological disorders that manifest as paroxysmal convulsive symptoms and/or changes in behavior and consciousness, mimicking ES but without associated cortical activity changes.[4–6] While PNES is the most commonly used term, the condition is increasingly referred to as a "functional neurological disorder."

The etiology and pathogenesis of PNES remain subjects of ongoing debate, with various proposed models emphasizing psychological or behavioral mechanisms as primary contributors.[7–9] Epidemiological studies using video-electroencephalography (v-EEG) to confirm diagnoses estimate an annual incidence of PNES at 4.90 per 100 000 individuals. Among patients referred to outpatient epilepsy centers, 5%–25% are diagnosed with PNES, while 10%–40% of patients in epilepsy monitoring units for pharmacoresistant epilepsy are ultimately found to have PNES.[4,5,7,8,10] According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), PNES is categorized under conversion disorders.[11]

Although v-EEG is considered the gold standard for distinguishing ES from PNES, it is limited by high costs, limited accessibility, and the need for prolonged hospitalizations. Moreover, recording PNES episodes often requires repeated hospital admissions.[4] These challenges underscore the need for alternative diagnostic methods, such as laboratory biomarkers, to improve accessibility and efficiency.

Recent studies have highlighted the potential of various biomarkers to enhance the understanding of neurological diseases. Among them, prolactin (PRL) and serum creatine kinase (CK) are the most widely used biomarkers for differentiating ES from PNES due to their high sensitivity and specificity. Other biomarkers, including neuron-specific enolase, brain-derived neurotrophic factor, ghrelin, leptin, leukocytosis, and lactate, have also been explored.[12–16]

Ubiquitin C-terminal hydrolase L1 (UCH-L1) and protein S100B are promising biomarkers released in response to neuronal and glial damage. Experimental and clinical studies have demonstrated elevated levels of UCH-L1 and S100B in the serum and cerebrospinal fluid of patients with ES.[17–19] S100B, first identified in the mid-1960s, was initially believed to be exclusive to nervous tissue, but subsequent studies revealed its presence in non-neural tissues as well.[20] The half-life

Key points

- This study compared postictal serum levels of UCH-L1 and S100B proteins in patients with epileptic seizures (ES), PNES, and healthy controls to investigate potential biomarkers for diagnosing PNES.
- All subjects with ES and PNES had normal brain MRI findings.
- v-EEG monitoring was performed for all subjects with PNES to confirm the diagnosis.
- The results showed a significant difference in UCH-L1 levels between patients with epilepsy and those with PNES or healthy controls. No significant differences were observed between PNES subjects and healthy controls ($p = 0.756$).
- No significant differences in postictal S100B protein levels were found between the examined groups.

of S100B protein has been reported to range from 60 to 120 min in patients with traumatic brain injury and approximately 90 min in patients with malignant melanoma.[21–23] Elevated S100B levels have been associated with structural epilepsy, such as post-stroke epilepsy, and temporal lobe epilepsy (TLE) in both adults and children.[23–27]

UCH-L1, a neuron-specific cytoplasmic enzyme highly enriched in neurons, has a relatively long half-life of 7 h in cerebrospinal fluid and 9 h in serum, providing stable levels for biomarker analysis after neuronal damage.[18,28] Research has implicated UCH-L1 in gene polymorphism dysfunction in neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease.[29,30] Additionally, UCH-L1 levels are known to increase following traumatic brain injury, stroke, aneurysmal subarachnoid hemorrhage, and neonatal hypoxic–ischemic encephalopathy. Studies have also demonstrated elevated UCH-L1 concentrations in the serum of patients with epilepsy.[18,19,31,32]

This study aims to investigate the postictal levels of UCH-L1 and S100B proteins as potential biomarkers for distinguishing ES from PNES, addressing the limitations of current diagnostic methods and contributing to the growing body of evidence supporting their diagnostic utility.

2 | MATERIALS AND METHODS

This prospective cohort pilot study compared postictal serum levels of UCH-L1 and S100B proteins in subjects with epileptic seizures (ES) to those in patients with psychogenic non-epileptic seizures (PNES) and healthy controls, aiming to identify novel biomarkers for distinguishing ES from PNES.

Subjects were included based on the following criteria:

Epileptic seizures group (ES): Subjects with generalized epileptic seizures or focal epileptic seizures evolving to bilateral tonic–clonic seizures, with normal brain MRI findings.

PNES group: Subjects with PNES confirmed by video-electroencephalography (v-EEG) monitoring and normal brain MRI findings, aged ≥18 years.

Control group: Thirty healthy individuals with no somatic, neurological, or psychiatric comorbidities and no chronic medication use. Blood samples were collected in the morning after hospital arrival, with no prior exercise or prolonged resting required.

Continuous v-EEG monitoring was conducted at the Department of Neurology, University Hospital Centre Zagreb, and School of Medicine, University of Zagreb, the Referral Centre of the Ministry of Health of the Republic of Croatia for Epilepsy, an affiliated member of the ERN EpiCARE network.

Subjects in the PNES group exhibited hyperkinetic seizures, non-motor seizures, or combinations thereof, without a predominant seizure type in the study population. PNES episodes during monitoring were characterized by clear clinical manifestations with no epileptiform EEG activity, only muscular artifacts. Some PNES episodes were triggered by verbal suggestion, such as informing patients that recording their seizures would aid in treatment, resulting in rapid PNES presentation. No use of nocebo methods was required.

The ES group included patients diagnosed per the International League Against Epilepsy (ILAE) criteria.[1] Structural causes of epilepsy, including tumors, strokes, and perinatal ischemic lesions, were excluded to ensure biomarker analysis focused solely on ictal events. All patients had MRI-negative epilepsy and no history of immunological or infectious causes. The frequency of seizures in this group was one to two events every 3 months on average. None of the subjects were on more than three antiseizure medications, and only four were pharmacoresistant and undergoing presurgical evaluation. Clinical characteristics and differences between groups are shown in Table 1.

Blood Sampling and Laboratory Procedures: Blood samples (3–4 mL) were collected from all subjects 30 min to 3 h post-seizure. Serum was collected in tubes without anticoagulant (Greiner Bio-One, Austria) and immediately placed on ice. Samples were centrifuged within 1 h at 4°C using a Heraeus Megafuge 1.0 R centrifuge (Thermo Fisher Scientific, USA). The serum was aliquoted into polypropylene containers (Eppendorf, Germany) and stored at −80°C until analysis.

S100B protein analysis: Serum concentrations were measured using the electro-chemiluminescence immunoassay (ECLIA) method with Elecsys® S100 reagents on a Cobas e801 device (Roche Diagnostics GmbH, Germany).

UCH-L1 analysis: Serum concentrations were determined using the enzyme-linked immunosorbent assay (ELISA).

For all patients, blood sampling occurred only once after the seizure. Subjects with epilepsy were on antiseizure medications, and more than 80% had blood sampling conducted during v-EEG monitoring, ensuring well-defined groups for comparison.

TABLE 1 Clinical characteristics and differences between groups (ES – epileptic seizures, PNES – Psychogenic non – epileptic seizures, n/a – nonapplicable

		ES	PNES	Healthy controls	
		N=32	N=36	N=30	P value
Age (years)*	Median (IQR)	39.0 (24.5-50.0)	36.0 (23.0-43.0)	37.0 (30.0-41.0)	0.389
Female gender**	N (%)	11 (34.4)	31 (86.1)	19 (63.3)	<0.001
Focal seizures with evolution to bilateral tonic – clonic seizures	N (%)	20 (62.5)			
Generalized tonic-clonic seizures	N (%)	12 (37.5)			
Pharmacoresistant epilepsy	N (%)	4 (12.5)			
More than 3 antiepileptic medications	N (%)	0 (0.0)			
Hyperkinetic PNES	N (%)		18 (50.0)		
Non - motor PNES	N (%)		14 (38.9)		
Hyperkinetic PNES and non - motor PNES	N (%)		4 (11.1)		
Arterial hypertension	N (%)	4 (12.5)	3 (8.3)		0.572
Dyslipidaemia	N (%)	1 (3.1)	1 (2.8)		1,000
Hypothireosis	N (%)	1 (3.1)	0 (0.0)		1,000
Head trauma	N (%)	3 (9.4)	3 (8.3)		1,000
Cardiovascular diseases	N (%)	2 (6.3)	2 (5.6)		1,000
Inflammatory bowel diseases	N (%)	1 (3.1)	1 (2.8)		1,000
Diabetes mellitus	N (%)	0 (0.0)	0 (0.0)		na
Age of diagnosis (years)*	Median (IQR)	17.0 (5.5-28.5)	34.5 (21.5-41.0)		<0.001
Time from attack to sampling (min)*	Median (IQR)	35.0 (30.0-62.5)	30.0 (30.0-55.0)		0.461
UCH-L1 (pg/mL)*	Median (IQR)	177.1 (21.8-995.4)	35.7 (0.0-310.8)	65.2 (0.0-276.8)	0.049
SB-100 (μg/L)*	Median (IQR)	0.04 (0.03-0.07)	0.04 (0.03-0.05)	0.04 (0.04-0.05)	0.515

*Kruskal-Wallis test, **Chi-squared test

2.1 | Statistical analysis

Data distribution was assessed using the Smirnov–Kolmogorov test. Quantitative variables were described with measures of central tendency and variability, and differences between groups were analyzed using the Student's *t*-test for independent samples or the Mann–Whitney *U* test for non-parametric distributions. Correlations between UCH-L1 and S100B concentrations were tested using Pearson's or Spearman's correlation coefficient, depending on data distribution.

Categorical variables were presented in contingency tables, with group differences analyzed using χ^2 or Fisher's exact test. Receiver-operating characteristic (ROC) curves were constructed for each biomarker, and sensitivity, specificity, and predictive values (positive and negative) were calculated. A p-value of <0.05 was considered statistically significant.

2.2 | Ethical considerations

The study received ethical approval from the Ethics Committee of University Hospital Centre Zagreb in January 2020 (Class 8.1-20/4-2, Number: 02/21 AG). Written informed consent was obtained from all participants.

3 | RESULTS

A total of 98 participants were included in the study: 32 subjects with epilepsy (21 men and 11 women), 36 subjects

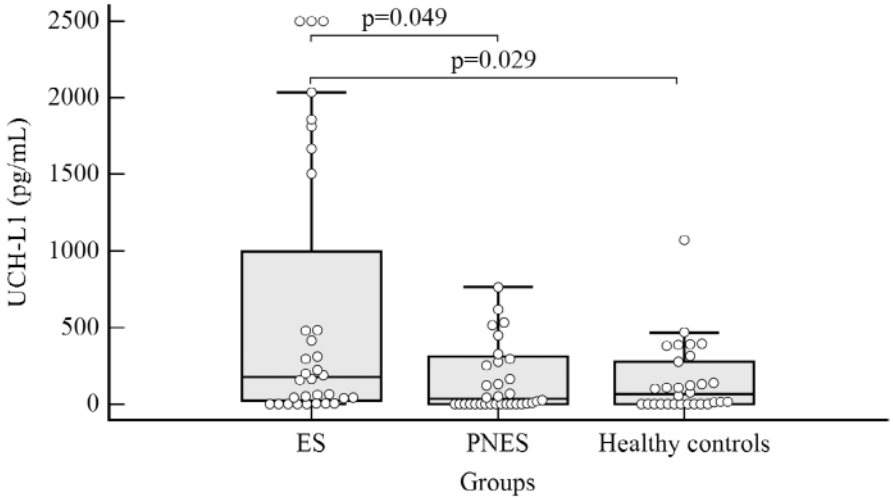

FIGURE 1 Differences in UCH-L1 (pg/mL) between the groups. ES, epileptic seizures; PNES, psychogenic non – epileptic seizures.

TABLE 2 Differences in UCH - L1 (pg/mL) between the studied groups:Kruskal-Wallis test

Groups		N	Min	Max	Centile 25.	Centile Median	Centile 75.
UCH - L1 (pg/mL)	Epilepsy	32	0,00	2500,00	13,70	177,09	1250,51
	PNES	36	0,00	2500,00	0,00	35,66	318,23
	Healthy controls	30	0,00	1073,05	0,00	65,18	286,07

	Kruskal-Wallis H	df	P
UCH - L1 (pg/mL)	3,878	1	0,049

with PNES (5 men and 31 women), and 30 healthy controls (11 men and 19 women). Our findings confirmed a significant difference in postictal UCH-L1 values among the three groups (Figure 1, Table 2). Post hoc analysis revealed that subjects with epilepsy had significantly higher UCH-L1 levels (pg/mL) compared to subjects with PNES ($p = 0.049$) and healthy controls ($p = 0.029$). However, no significant difference was observed between PNES and healthy controls ($p = 0.756$) (Table 3). There was no significant difference in S100B protein values between the examined groups ($p = 0.515$) (Figure 2). The epilepsy group had a significantly higher proportion of men (65.6%) compared to the PNES group (13.9%, $p < 0.001$) and the healthy controls (36.7%, $p = 0.041$). Conversely, the PNES group had a significantly higher proportion of women compared to healthy controls (86.1% vs. 63.3%, $p = 0.044$), consistent with epidemiological data indicating that PNES is more frequent in women.[9,41]

No significant differences in UCH-L1 or S100B protein values were observed between male and female participants. We compared the prevalence of psychiatric diagnoses, previously established by a psychiatrist based on the ICD-10 classification, between the groups. The prevalence of psychiatric diagnoses did not differ significantly among the groups ($p = 0.143$). Anxiety, depression, and post-traumatic stress disorder were the most common psychiatric conditions across all groups. In the epilepsy group, 22 participants (68.75%) did not have a psychiatric diagnosis, while 10 participants (31.25%) did. In the PNES group, 18 participants (50%) had a psychiatric diagnosis, and 18 (50%) did not.

A significant difference in the age at diagnosis was observed between the epilepsy and PNES groups ($p < 0.001$). The median age of diagnosis for PNES was 34.5 years (interquartile range [IQR]: 21.3–41.5 years), while for epilepsy, it was 16.0 years (IQR: 5.3–28.8 years).

All subjects in both the ES and PNES groups had normal MRI findings of the brain. Additionally, all PNES participants underwent v-EEG monitoring, which was evaluated by an epileptologist to confirm the diagnosis of PNES.

4 | DISCUSSION

This prospective cohort pilot study examined the postictal levels of two potential biomarkers, UCH-L1 and protein S100B, to differentiate epileptic seizures from psychogenic non-epileptic seizures. The results demonstrated a significant difference in postictal UCH-L1 levels between the

TABLE 3 Post-hoc analysis of differences in UCH - L1 (pg/mL) between the groups: Dunn's test.

A		N	Mean Rank	Sum of Ranks	z	P
UCH - L1 (pg/mL)	Epilepsy	32	39.47	1263.00	-1.969	0.049
	PNES	36	30.08	1083.00		

B		N	Mean Rank	Sum of Ranks	z	P
UCH - L1 (pg/mL)	Epilepsy	32	36.31	1162.00	-2.185	0.029
	Healthy controls	30	26.37	791.00		

C		N	Mean Rank	Sum of Ranks	z	P
UCH - L1 (pg/mL)	PNES	36	34.15	1229.5	-0.310	0.756
	Healthy controls	30	32.72	981.00		

Subjects with epilepsy have a significantly higher value of postictal UCH - L1 (pg/mL) compared to subjects with PNES (P=0.049) and compared to healthy controls (P=0.029), while there are no significant differences between subjects with PNES and healthy controls (P=0.756).

Subjects with epilepsy have a significantly higher value of UCH - L1 (pg/mL) compared to subjects with PNES (P=0.049) and compared to healthy controls (P=0.029), while there are no significant differences between subjects with PNES and healthy controls (P=0.756).

(ES – epileptic seizures, PNES – Psychogenic non – epileptic seizures)

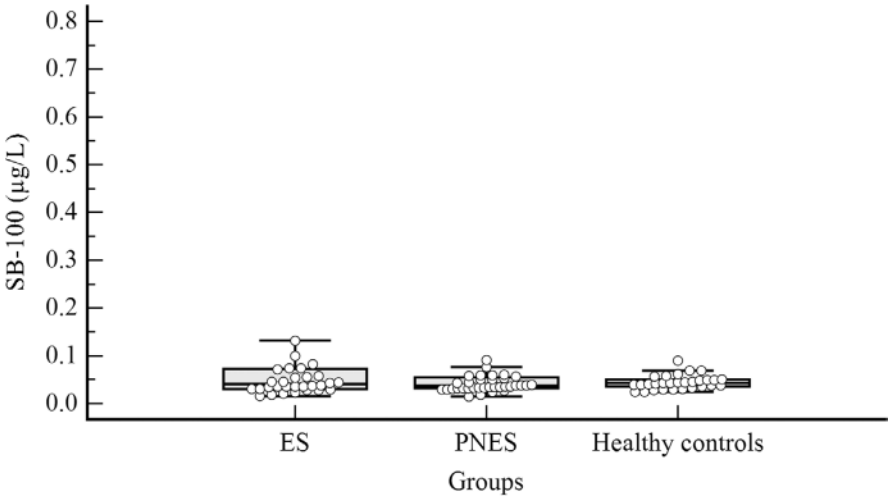

FIGURE 2 Differences in S100B (µg/L) between the studied groups. No significant difference in S100B protein values between the examined groups was demonstrated ($p = 0.515$). ES, epileptic seizures; PNES, psychogenic non – epileptic seizures.

examined groups. Subjects with ES exhibited significantly higher postictal UCH-L1 levels (pg/mL) compared to subjects with PNES and healthy controls, whereas no significant differences were found between the PNES group and healthy controls. In contrast, no significant differences in postictal S100B levels were detected across the examined groups.

The study's primary inclusion criterion for both ES and PNES groups was the presence of normal MRI findings of the brain. This criterion was chosen to eliminate potential confounding conditions such as tumors, strokes, subarachnoid hemorrhage, or traumatic brain injury, which independently elevate UCH-L1 and S100B levels. This approach represents a novel aspect of the study and ensures more accurate biomarker evaluation.

Our findings align with prior studies[18,19,32] that included subjects with structural brain changes detected on MRI, such as temporal sclerosis, parenchymal gliosis, low-grade tumors, cortical dysplasia, and infarctions. These studies also demonstrated elevated postictal UCH-L1 levels in structural epilepsy cases. By extending this research to individuals with epilepsy and normal MRI findings, we confirmed that postictal UCH-L1 levels are elevated in both structural and non-structural epilepsy compared to PNES.

Given the half-life of protein S100B (30 min) and UCH-L1 (7 h in cerebrospinal fluid, 9 h in serum), we standardized blood sampling between 30 min and 3 h after seizure onset. This ensured reliable biomarker measurement while avoiding false positives or negatives. Notably, the

median sampling time for ES subjects was 35 min and for PNES subjects was 30 min, with no significant difference in sampling times between groups. Over 80% of ES subjects experienced seizures during hospital stays, ensuring prompt sampling.

Our study did not establish an association between postictal S100B levels and epilepsy compared to PNES. The lack of significant findings could be attributed to the complexity of S100B, a multigene family of calcium-binding proteins expressed in diverse neural and non-neural tissues. This broad distribution may contribute to previously reported false positives in epilepsy research, particularly in cases involving comorbidities like traumatic brain injury. Future studies should explore S100B's role as a biomarker for epilepsy in subjects with normal MRI findings and without comorbid conditions.

Our study revealed that eight subjects with epilepsy had significantly elevated UCH-L1 levels. These subjects, aged 21–58 years, had been diagnosed with epilepsy for over a decade. Five had focal epilepsy evolving to bilateral tonic–clonic seizures, while three had generalized tonic–clonic seizures. All were MRI-negative for structural brain abnormalities. Notably, four were pharmacoresistant and undergoing presurgical evaluation, while the others achieved seizure freedom with consistent antiepileptic medication. Sampling times for these subjects ranged from 30 to 95 min post-seizure.

As a pilot study, the statistical significance of UCH-L1 findings may have been influenced by the small sample size, particularly the eight subjects with elevated levels. While these results support the hypothesis that UCH-L1 can distinguish PNES from ES, larger-scale studies are necessary to validate its clinical utility. Although promising, the small sample size limits the immediate clinical applicability of UCH-L1 as a differentiating biomarker.

Epilepsy biomarkers should reliably capture the disease's heterogeneity and pathogenesis, enabling patient characterization and targeted treatment approaches. This study focused on one aspect of epilepsy, yielding promising results for UCH-L1 as a biomarker. Future research should expand sample sizes, refine inclusion criteria, and consider additional factors, such as seizure types and comorbidities, to establish these biomarkers' clinical roles.

5 | LIMITATIONS

This study investigated different biomarkers in patients with epilepsy and compared them to those with PNES. However, previous researches on UCH-L1 and protein S100B have employed varying methodologies, particularly regarding the timing of blood sampling, study populations, and the inclusion of concomitant neurological conditions. These methodological differences limit the generalizability of our findings and the potential clinical implementation of UCH-L1 and protein S100B as biomarkers for epilepsy.

A significant limitation of our study is that the results are specific to epileptic seizures in patients with normal brain MRI findings. This focus excludes other aspects of the heterogeneity and pathogenesis of epilepsy. Furthermore, the relatively small sample size restricts the applicability of our findings to the broader epilepsy population. Larger-scale studies are needed to validate these biomarkers' clinical utility and explore their relevance in diverse epilepsy subtypes.

6 | CONCLUSION

The results of our study demonstrated a significant difference in postictal UCH-L1 levels between subjects with epilepsy and those with PNES or healthy controls (Figure 1). In contrast, no significant differences in postictal S100B protein levels were observed between the examined groups ($p = 0.515$) (Figure 2).

By excluding conditions that could independently elevate these biomarkers, our research focused specifically on UCH-L1 and S100B values in subjects with epileptic seizures and PNES, all of whom had normal brain MRI findings. The lack of significant findings for S100B protein raises questions about its reliability as a biomarker for epilepsy, highlighting the need for further investigation.

We recommend conducting future studies using similar criteria on larger participant samples to validate our findings and explore the potential clinical utility of UCH-L1 as a biomarker for distinguishing epilepsy from PNES.

AUTHOR CONTRIBUTIONS

Biljana Dapic Ivancic: Original draft preparation (lead); writing – review and editing; data curation; formal analysis (lead); visualization; validation. **Zeljka Petelin Gadze:** review, visualization; conceptualization; validation. **Lana Ganoci:** data curation; formal analysis; **Petra Nimac Kozina:** Investigation; **Dunja Rogic:** data curation; formal analysis; **Maja Zivkovic:** Project administration (lead); conceptualization; supervision; writing – review.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

INFORMED CONSENT

Informed consent was obtained from all subjects included in the study.

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